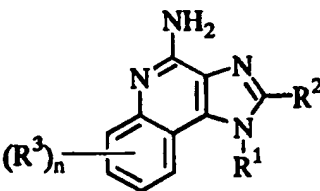




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/47	A1	(11) International Publication Number: WO 98/48805 (43) International Publication Date: 5 November 1998 (05.11.98)
(21) International Application Number: PCT/JP98/01841 (22) International Filing Date: 22 April 1998 (22.04.98) (30) Priority Data: 9/123146 25 April 1997 (25.04.97) JP (71) Applicants (for all designated States except US): SUMITOMO PHARMACEUTICALS COMPANY, LIMITED [JP/JP]; 2-8, Doshomachi 2-chome, Chuo-ku, Osaka-shi, Osaka 541-0045 (JP). JAPAN ENERGY CORPORATION [JP/JP]; 10-1, Toranomom 2-chome, Minato-ku, Tokyo 105-0001 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): OCHI, Hiroshi [JP/JP]; 9-12-105, Miyano-cho, Takasaki-shi, Osaka 569-0081 (JP). WATANABE, Takamasa [JP/JP]; 4-15-506, Maruhashi-cho, Nishinomiya-shi, Hyogo 662-0831 (JP). TOMIZAWA, Hideyuki [JP/JP]; 6-12-1-2-306, Shikatebukuro, Urawa-shi, Saitama 336-0031 (JP). GOTO, Yuso [JP/JP]; 4-16-302, Hikawa-cho 1-chome, Toda-shi, Saitama 335-0027 (JP).		(74) Agents: AOYAMA, Tamotsu et al.; Aoyama & Partners, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540-0001 (JP). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PHARMACEUTICAL COMPOSITION FOR SUPPRESSING TYPE 2 HELPER T CELL IMMUNE RESPONSE <div style="text-align: center;">  (1) </div> (57) Abstract <p>A pharmaceutical composition for suppressing Th2 type immune response comprising as active ingredient a compound represented by formula (1), wherein R¹ is alkyl, cycloalkyl, hydroxyalkyl, acyloxyalkyl, aralkyl, substituted aralkyl, phenyl, or substituted phenyl; R² is H or alkyl; R³ is alkoxy, halogen or alkyl; n is 0 to 2; specifically 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine, or a pharmaceutically acceptable acid salt thereof, and a method for treating or preventing a disease caused by abnormal activation of Th2 type immune response, such as asthma, allergic dermatitis, allergic rhinitis or systemic lupus erythematosus, which comprises administering a therapeutically effective amount of the compound (1) to a patient in need thereof.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

DESCRIPTION

PHARMACEUTICAL COMPOSITION FOR
SUPPRESSING TYPE 2 HELPER T CELL IMMUNE RESPONSE

5

TECHNICAL FIELD

The invention is directed to a pharmaceutical composition having less side effects for treating or preventing allergic diseases such as asthma, allergic dermatitis, allergic rhinitis, or an autoimmune disease such as systemic lupus erythematosus by suppressing immune response of type 2 helper T cell (hereinafter "Th2") and enhancing immune response of type 1 helper T cell (hereinafter "Th1") comprising a therapeutically effective amount of a compound having structure of 1H-imidazo[4,5-c]quinolin-4-amine. The invention also directs to a method of treating or preventing allergic diseases or autoimmune diseases.

10

BACKGROUND ART

Mosmann et al. first suggested that a lymphocyte, called a helper T cell (hereinafter "Th"), which plays a major role in the immune response is classified into two subsets. They classified mouse Th clones into the two subsets, Th1 and Th2, depending on cytokine production pattern (J. Immunol. (1986) 136: 2348-2357).

20

Recently the classification of Th1/Th2 is not only a classification of helper T cell subsets, but also the concept by which an immune response can be categorized into a Th1 type immune response and a Th2 type immune response in vivo. In the Th1 type immune response, cytokines produced by an activated Th1, such as interferon- γ

25

(IFN- γ), interleukin 2 (IL-2) and so on, play a major role. It is reported that the Th1 type cytokines activate a macrophage, a natural killer cell and so on, and IL-12 is produced from the activated macrophage. IL-12 augments the activation of Th1. Th1 is considered to be related to cellular immunity such as protection of a virus or a bacterium infection through the above mechanism. In Th2 type immune response, cytokines produced from an activated Th2 cell, such as IL-4, IL-5 and so on, play a major role. It is reported that the Th2 cytokines relate to humoral immunity that includes antibody production from B cells (including IgE).

Th2 is considered to be a cell that controls the allergic response, since Th2 produces cytokines such as IL-4 and IL-5 which are involved in the allergic response. For example, typical Th2 type cytokine, IL-4 makes B cells to produce IgE. IL-4 also makes endothelial cells to express VCAM-1, which is important in inducing eosinophils to adhere to endothelial cell and to invade into tissues (Pharmacia (1993) 29: 1123-1128). Recently IL-4 is reported to be a differentiation and proliferation factor of Th2. IL-5 which is also a Th2 type cytokine is considered to be an elicitation factor of the allergic response, since IL-5 makes eosinophils to differentiate, to proliferate, to migrate and to activate.

As described above, Th2 is recognized as a cell that mainly controls both an immediate phase allergic reaction that relates to an IgE antibody and a mast cell and a late phase allergic reaction that relates to an eosinophil. Therefore it is considered that allergy is a disease caused by abnormal activation of Th2 type immune response. Th2 and

Th2 type cytokines, such as IL-4 and IL-5, are found in a local allergic lesioned site.

It is important for treating or preventing allergic reaction to suppress the Th2 type immune response. In other words, If a drug that can suppress the Th2 type immune response is developed, it can be an effective medicine for treating or preventing allergic diseases.

It is considered that the late phase allergic reaction play an important role especially in severe asthma, atopic dermatitis and so on. Anti-allergic agents, which are available now, suppress only immediate phase allergic reaction and do not have sufficient clinical effects. Only steroids are effective for severe asthma and atopic dermatitis and have been frequently used. Long term administration of steroids may cause side effects such as steroid dermatitis, opportunistic infection, and dysfunction of the adrenal cortex. So it is expected to develop an agent that can suppress Th2 type immune response and can treat or prevent both of late phase allergic reaction and immediate phase allergic reaction.

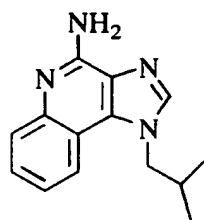
As described above when an agent that has less side effects is considered, it is preferable to develop an agent that not only can suppress the Th2 type immune response, but also can enhance the Th1 type immune response. Since Th1 produces $\text{INF-}\gamma$ and plays a major role in the protection of virus and bacterium infection, it is very preferable that a suppressor of the Th2 type immune response also has a property of enhancing Th1 type immune response. An immuno-suppressor such as cyclosporin or FK506 suppresses not only activation of Th2, but also suppresses activation of Th1 non-specifically,

and which also causes opportunistic infection. Such side effects have become a serious clinical problem.

As described above, if an agent that can suppress Th2 type immune response and can enhance Th1 type immune response is developed, it will be an effective medicine, which has less side-effects, for allergic diseases.

Autoimmune diseases, such as systemic lupus erythematosus, are accompanied by enhancement of antibody production and humoral immunity and it is considered that such diseases result from abnormal activation of Th2 type immune response (Medical Immunology (1988) 15: 401). Therefore, it is also considered that such an agent described above can be effective for the prevention and treatment of autoimmune diseases.

Known activities of a compound having the structure of the 1H-imidazo[4,5-c]quinolin-4-amine such as Imiquimod of the following formula are described below.



It is reported that Imiquimod exhibits an anti-herpes simplex virus activity in the guinea pig (Antimicrob. Agents Chemother. (1989) 33: 1511-1515). It is also reported that Imiquimod shows anti-viral activities in cytomegalovirus (Antimicrob. Agents Chemother. (1988) 32: 678-683) and arbovirus infection (Adv. Biosci. (1988) 68: 51-63). It is reported that such anti-viral activities come from an activity of

enhancing the production of IFN- α (Antiviral Res. (1988) 10: 209-224).

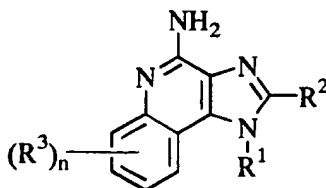
Imiquimod shows an activity of enhancing production of IFN- α in vitro and in vivo mouse models (Journal of Leukocyte Biology (1994) 55: 234-240).

5 It is also reported that Imiquimod also shows an anti-cancer activity in various models (Cancer Res. (1992) 52: 3528-3533). It is further reported that Imiquimod enhances production of IL-1, IL-6, IL-8 and TNF- α in vitro and in vivo mouse experimental models (Journal of Leukocyte Biology (1994) 55: 234-240). It is suggested that a part of
10 the anti-cancer activity comes from the activity of inducing the TNF- α production.

Although it is reported that Imiquimod has anti-viral and anti-cancer activities and enhances the production of INF- α and TNF- α , it has not been reported nor suggested that Imiquimod suppresses
15 production of IL-4 and IL-5 from Th2 and enhances production of IFN- γ . It also has not been suggested that Imiquimod suppresses the Th2 type immune response and can be applied for treating or preventing allergic diseases and autoimmune diseases caused by abnormal activation of Th2 type immune response.

20 DISCLOSURE OF INVENTION

The present invention is directed to a pharmaceutical composition for suppressing Th2 type immune response comprising a therapeutically effective amount of a compound represented by the formula (1):



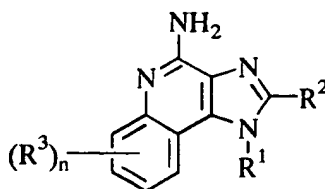
wherein R¹ is a straight or branched chain alkyl having 1 to 10 carbon atoms; a cycloalkyl having 3 to 7 carbon atoms; a hydroxyalkyl having 1 to 6 carbon atoms; an acyloxyalkyl wherein the alkyl moiety has 1 to 6 carbon atoms and the acyloxy moiety is an alkanoyloxy having 2 to 4 carbon atoms or benzoyloxy; an aralkyl; a substituted aralkyl; a phenyl; or a substituted phenyl;

R² is hydrogen atom or an alkyl having 1 to 8 carbon atoms;

R³ is an alkoxy having 1 to 4 carbon atoms, a halogen atom or an alkyl having 1 to 4 carbon atoms; and

n is an integer from 0 to 2; or a pharmaceutically acceptable acid salt thereof.

The present invention is also directed to a method of treating or preventing a disease caused by abnormal activation of the Th2 type immune response comprising administering a therapeutically effective amount of a compound represented by the formula (1):



wherein R¹ is a straight or branched chain alkyl having 1 to 10 carbon atoms; a cycloalkyl having 3 to 7 carbon atoms; a hydroxyalkyl having 1 to 6 carbon atoms; an acyloxyalkyl wherein the alkyl moiety has 1 to 6 carbon atoms and the acyloxy moiety is an alkanoyloxy having 2 to 4

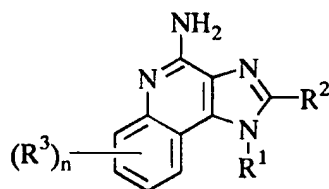
carbon atoms or benzyloxy; an aralkyl; a substituted aralkyl; a phenyl;
or a substituted phenyl;

R² is hydrogen atom or an alkyl having 1 to 8 carbon atoms;

5 R³ is an alkoxy having 1 to 4 carbon atoms, a halogen atom or an alkyl
having 1 to 4 carbon atoms; and

n is an integer from 0 to 2; or a pharmaceutically acceptable acid salt
thereof to a patient in need thereof.

The present invention is directed to a pharmaceutical
composition for treating or preventing an allergic disease or an
10 autoimmune disease caused by abnormal activation of immune
response of Th2 side comprising a therapeutically effective amount of a
compound represented by the formula (1):



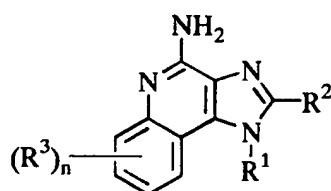
wherein R¹ is a straight or branched chain alkyl having 1 to 10 carbon
atoms; a cycloalkyl having 3 to 7 carbon atoms; a hydroxyalkyl having 1
15 to 6 carbon atoms; an acyloxyalkyl wherein the alkyl moiety has 1 to 6
carbon atoms and the acyloxy moiety is an alkanoyloxy having 2 to 4
carbon atoms or benzyloxy; an aralkyl; a substituted aralkyl; a phenyl;
or a substituted phenyl;

R² is hydrogen atom or an alkyl having 1 to 8 carbon atoms;

20 R³ is an alkoxy having 1 to 4 carbon atoms, a halogen atom or an alkyl
having 1 to 4 carbon atoms; and

n is an integer from 0 to 2; or a pharmaceutically acceptable acid salt
thereof to a patient in need thereof.

The present invention is also directed to a pharmaceutical composition for treating or preventing an allergic disease or an autoimmune disease caused by abnormal activation of immune response of Th2 side comprising a therapeutically effective amount of a compound represented by the formula (1):



wherein R¹ is a straight or branched chain alkyl having 1 to 10 carbon atoms; a cycloalkyl having 3 to 7 carbon atoms; a hydroxyalkyl having 1 to 6 carbon atoms; an acyloxyalkyl wherein the alkyl moiety has 1 to 6 carbon atoms and the acyloxy moiety is an alkanoyloxy having 2 to 4 carbon atoms or benzoyloxy; an aralkyl; wherein the phenyl may be substituted by one or more than one substituents selected from the group consisting of an alkyl having 1 to 4 carbon atoms and an alkoxy having 1 to 4 carbon atoms;

R² is hydrogen atom or an alkyl having 1 to 8 carbon atoms;

R³ is independently selected from the group consisting of an alkoxy having 1 to 4 carbon atoms, a halogen atom and an alkyl having 1 to 4 carbon atoms; and

n is an integer from 0 to 2 with the proviso that if n is 2, two R³ have no more than 6 carbon atoms; or a pharmaceutically acceptable acid salt thereof to a patient in need thereof.

BEST MODE FOR CARRYING OUT THE INVENTION

A compound or a pharmaceutically acceptable salt thereof of formula (1) may be manufactured by a method known to a person of

ordinary skill in the art. For example, it may be manufactured by a method described in Tokkou-Hei 5-86391 (JP5-86391B).

Examples of the straight chain alkyl having 1 to 10 carbon atoms of R¹ are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and the like. The branched chain alkyl having 1 to 10 carbon atoms includes a branched chain alkyl having 3 to 10 carbon atoms.

Examples of the branched chain alkyl group having 3 to 10 carbon atoms of R¹ are 1-methylethyl, 2-methylpropyl, 1-methylpropyl, 1,1-dimethylethyl, 3-methylbutyl, 4-methylpentyl and the like. Examples of the cycloalkyl having 3 to 7 carbon atoms of R¹ are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

A hydroxyalkyl having 1 to 6 carbon atoms of R¹ includes a straight chain hydroxyalkyl having 1 to 6 carbon atoms, a branched chain hydroxyalkyl having 3 to 6 carbon atoms and the like. Examples of the straight chain hydroxyalkyl having 1 to 6 carbon atoms are hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 2-hydroxybutyl, 2-hydroxypentyl, 2-hydroxyhexyl and the like. Examples of the branched chain hydroxyalkyl having 3 to 6 carbon atoms are 2-hydroxy-2-methylpropyl and the like.

Examples of the alkyl moiety having 1 to 6 carbon atoms in the acyloxyalkyl of R¹ are methyl, ethyl, propyl, butyl, pentyl, hexyl and the like. The acyloxy moiety in the acyloxyalkyl of R¹ includes an alkanoyloxy having 2 to 4 carbon atoms, benzoyloxy and the like. Examples of the alkanoyloxy having 2 to 4 carbon atoms are acetyloxy, propanoyloxy, butanoyloxy and the like. Specific examples of the acyloxyalkyl are 2-acetyloxypropyl, 2-acetyloxy-2-methylpropyl, 2-

benzoyloxy-2-methylpropyl and the like.

The aralkyl of R^1 includes an aralkyl having 7 to 10 carbon atoms. Specific examples of the aralkyl are benzyl, phenethyl and the like.

5 Examples of a substituent of the substituted aralkyl are an alkoxy having 1 to 4 carbon atoms, a halogen and the like. Examples of the alkoxy having 1 to 4 carbon atoms are methoxy, ethoxy, propoxy, butoxy and the like. Examples of the halogen are fluorine, chlorine, bromine and the like. The substituted aralkyl may have one or more
10 substituents independently on the aryl moiety.

 Examples of a substituent of the substituted phenyl are an alkoxy having 1 to 4 carbon atoms, a halogen and the like. Examples of the alkoxy having 1 to 4 carbon atoms are methoxy, ethoxy, propoxy, butoxy and the like. Examples of the halogen are fluorine, chlorine,
15 bromine and the like. The substituted phenyl may have one or more substituents independently.

 The alkyl having 1 to 8 carbon atoms of R^2 includes a straight chain alkyl having 1 to 8 carbon atoms, a branched chain alkyl having 3 to 8 carbon atoms. Examples of the straight chain alkyl having 1 to
20 8 carbon atoms are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and the like. Examples of the branched chain alkyl having 3 to 8 carbon atoms are 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1-methylbutyl, 1,1-dimethylethyl and the like.

 Examples of the alkoxy having 1 to 4 carbon atoms of R^3 are
25 methoxy, ethoxy, propoxy, butoxy and the like. Examples of the halogen of R^3 are chlorine, fluorine, bromine and the like. If n is 2, two

R³ may be same or different.

The examples of pharmaceutically acceptable acid salt are an inorganic acid and an organic acid such as hydrogen chloride, sulfuric acid, acetic acid, oxalic acid, ascorbic acid and so on.

5 A preferred embodiment of a compound represented by the formula (1) is that R¹ is 2-methylpropyl or 2-hydroxy-2-methylpropyl, and R² is hydrogen, methyl or ethyl and n is 0.

10 A particularly preferred embodiment of a compound of the formula (1) includes 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (Imiquimod), R842, S-27609 (Journal of Leukocyte Biology (1995) 58: 365-372) and S-28463 (Antiviral Research (1995) 28: 253-264).

15 The pharmaceutical composition of the present invention may further comprise other pharmaceutical agents. The pharmaceutical composition of the present invention may be used with other pharmaceutical agent. Such pharmaceuticals agent includes a bronchodilator, an anti-allergic agent, a steroid and the like that is available or known to a person of ordinary skill in the art and is used for treating allergic diseases. As described above a steroid is often used for treating severe asthma and atopic dermatitis. As pointed out
20 above long-term administration of steroid causes various side-effects such as steroid dermatitis, opportunistic infection, adrenocortical insufficiency, rebound of stopping administration and so on. It is expected that use of a specific suppressor of Th2 type immune response of the present invention with a steroid can reduce the amount of steroid
25 administered and can also reduce the side-effects.

The pharmaceutical composition of this invention can be

administered in any number of conventional dosage forms, e.g., topical, oral, parenteral, rectal, transdermal, nasal and the like. Oral or rectal dosage forms include capsules, tablets, pills, powders, cachets, and suppositories. Liquid oral dosage forms include solutions and
5 suspensions. Parenteral preparations include sterile solutions and suspensions. Topical dosage forms can be creams, ointments, lotions, transdermal devices (e.g., of conventional patch or matrix type) and the like.

The above described dosage forms can be prepared with
10 conventional pharmaceutically acceptable excipients and additives, using conventional techniques. Such pharmaceutically acceptable excipients and additives are intended to include carriers, binders, flavorings, buffers, thickeners, coloring agents, stabilizing agents, emulsifying agents, dispersing agents, suspending agents, perfumes,
15 preservatives, lubricants, etc.

Suitable pharmaceutically acceptable solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium
carboxymethylcellulose, low melting waxes, cocoa butter and the like.

20 Capsules can be made wherein the active compound is filled into the capsules together with a pharmaceutically acceptable carrier. The active ingredient of this invention can be mixed with pharmaceutically acceptable excipients or be used in finely divided powder form without excipients for inclusion into the capsules. Similarly, cachets are
25 included.

Liquid form preparations include solutions, suspensions and

emulsions such as water or water-propylene glycol solutions for parenteral injection. Liquid form preparations can also be formulated in a solution in polyethylene glycol and/or propylene glycol, which may contain water. Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding thereto suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the active component in finely divided form in water with viscous materials, i.e. pharmaceutically acceptable natural and synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose and other well-known suspending agents.

Formulations for topical application may include the above liquid forms, as well as creams, aerosols, sprays, dusts, powders, lotions and ointments which are prepared by combining an active ingredient according to this invention with conventional pharmaceutically acceptable diluents and carriers commonly used in topical, dry, liquid, cream and aerosol formulations. Ointment and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Such bases may, thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as peanut oil or castor oil. Thickening agents which may be used according to the nature of the base include soft paraffin, aluminum stearate, cetostearyl alcohol, propylene glycol, polyethylene glycols, woolfat, hydrogenated lanolin, beeswax, etc.

Lotions may be formulated with an aqueous or oil base and will,

in general, also include one or more of pharmaceutically acceptable stabilizing agents, suspending agents, emulsifying agents, dispersing agents, thickening agents, coloring agents, perfumes and the like.

Powders may be formed with the aid of any suitable
5 pharmaceutically acceptable powder base, e.g., talc, lactose, starch, etc. Drops may be formulated with an aqueous base or nonaqueous base comprising one or more pharmaceutically acceptable dispersing agents, suspending agents, solubilizing agents, etc.

The topical pharmaceutical composition may also include one
10 or more preservatives or bacteriostatic agents, e.g., methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chloride, etc.

The topical pharmaceutical compositions may also contain an active compound of this invention in combination with other active
15 ingredients such as antimicrobial agents, particularly antibiotics, anesthetics, analgesics, and antipruritic agents.

For intranasal administration of the compound of formula (1) may be used, for example, as a liquid spray, as a powder or in the form of drops.

20 For administration by inhalation of the compound of formula (1) are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2-tetrafluoroethane, carbon dioxide or
25 other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Capsules and cartridge of e.g. gelatin for use in inhaler or insufflator may be formulated containing a powder mix of a compound of the formula (1) and a suitable powder base such as lactose or starch.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dosage form and as such are used to provide a single liquid dosage unit. Alternatively, sufficient solid may be provided so that after conversion to liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of liquid form preparation as with a syringe, teaspoon or volumetric container. When multiple liquid doses are prepared, it is preferred to maintain the unused portion of said liquid doses under conditions which retard possible decomposition. The solid form preparations intended to be converted to liquid form may contain, in addition to the active ingredient, pharmaceutically acceptable flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents and the like. The solvent utilized for preparing the liquid form preparation may be water, isotonic water, ethanol, glycerin, propylene glycol and the like as well as mixtures thereof. Naturally, the solvent utilized will be chosen with regard to the route of administration, for example, liquid preparations containing large amount of ethanol are not suitable for parenteral use.

The active ingredient of this invention may also deliverable transdermally for systemic distribution. As a transdermal patch of the

matrix or reservoir type as are conventional in the art for this purpose.

The compound represented by the formula (1) can also be formulated as depot preparations. Such long acting formulation can be administered by implantation (for example subcutaneously or intra-
5 muscularly) or by intramuscular injection. Thus, for example, the compound can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in a pharmaceutically acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example as a sparingly soluble salt.

10 The compound represented by the formula (1) can also be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic acid and polyglycolic acid, polyepsilon caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals,
15 polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

A composition of the invention comprises a therapeutically effective amount of a compound represented by the formula (1) in combination with a pharmaceutically acceptable carrier material.

20 The composition of the invention may be administered by any conventional mode of administration by employing a therapeutically effective amount of a compound represented by the formula (1) for such mode. The dosage may be varied depending upon the requirements of the patient in the judgment of attending clinician, the severity of the
25 condition being treated and the particular compound being employed. Determination of the proper dosage for a particular situation is within

the skill of the art. Treatment can be initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter the dosage should be increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dose may be divided and administered in portions during the day if desired.

An oral pharmaceutical composition of present invention can be administered once a day or more than once a day. In the particular case of an adult, an amount of dosage for said oral administration is selected from ranging about 1 to about 200mg, and preferred range is from about 10 to about 50mg. A pharmaceutical composition of the present invention for injection can be administered once a day or more than once a day. An amount of dosage for said administration for injection is selected from ranging about 0.1 to about 100mg, and preferred range is from about 3 to about 30mg.

Diseases which can be treated or prevented according to the present invention include asthma, allergic dermatitis, allergic rhinitis and systemic lupus erythematosus caused by abnormal activation of the Th2 type immune response.

The present invention is further illustrated by the following examples, but the present invention is not limited to the examples.

Example 1

An activity of Imiquimod to the production of cytokines from antigen stimulated lymph node cells

1. Experimental method

BALB/c mouse was purchased from Nihon Charles River

(Yokohama, Japan) and female mice of 8 week-old were used for the experiment.

2. Medium

To RPMI1640 medium, fetal bovine serum (Characterized, code No. A-1115-L, HyClone Lab., Logan, Utah) inactivated by heated to 56°C for 30 minutes was added to become 10 % and 2-mercaptoethanol was added to become 0.05 mM.

3. Agent

Imiquimod that was synthesized by the method described in Tokkou-Hei 5-86391 was solved in dimethylsulfoxide (Nakarai Tesque Code No. 11J) to become 100 mM.

4. Sensitization to mouse and preparation of lymph node cells

10 mg of KLH (Keyhole Limpet Hemocyanin) in 2.5 ml of saline and 2.5 ml of Freund's complete adjuvant (Difco Lab., Detroit, Michigan, Code No. 3113-60-5) were mixed and homogenized, and the homogenate was subcutaneously administered to mouse foot pad (0.1ml/head). 8 days later popliteal lymph node was picked up and cell suspension was prepared.

5. Production of cytokines by stimulation of antigen

The KLH (0.1mg/ml) and imiquimod solution prepared in 3 was added to lymph node cell suspension (2.5×10^6 cells/ml) prepared in 4, and was cultured for four days at 37°C under 5 % CO₂ atmosphere (0.15 ml/well). The cytokines in the supernatant was measured by ELISA described in 6. An amount of IL-4 and IL-5 that are representatives of Th2 type cytokines and an amount of IFN-γ that is a representative of Th1 type cytokines were measured.

6. Quantitative measurement of IL-4, IL-5 and IFN- γ by ELISA

Quantitative measurement of IL-4 was done by ELISA described below. Rat anti-mouse-IL-4 antibody was used as a primary antibody (Pharmingen, San Diego, CA, Code No. 18031D, 0.5 mg/ml) and was
5 diluted to 250 times by carbonate buffered solution. 50 μ l of the solution was put into 96-well plate (Falcon 3912, Becton Dickinson and Company, Franklin Lakes, NJ). The plate was incubated at 4°C over a night. The plate was blocked by using PBS (-) containing 3 % of BSA. The plate was rinsed, dried and stored at -20°C. 50 μ l of the
10 supernatant was added to each well of primary antibody coated plate and incubated for four hours at room temperature. Recombinant mouse IL-4 (Pharmingen, San Diego, CA, Code No. 18042D, 0.5 mg/ml) was used to make a calibration curve. Biotinated rat anti-mouse-IL-4 antibody (Pharmingen, Code No. 18042D, 0.5 mg/ml) was diluted 500
15 times by PBS(-) containing 0.1 % BSA and was used as secondary antibody. After the plate was rinsed, 100 μ l of the solution of biotinated rat anti-mouse-IL-4 antibody was added to each well and was incubated for an hour at room temperature. Secondary antibody bound to the plate was detected by using streptoavidin phosphatase
20 (Kirkegaard & Perry Lab., Gaithersburg, MD, Code No. 15-3000) (0.25 mg/ml, 100 μ l/well). After the plate was incubated for an hour at 37°C, PNPP substrate (p-nitrophenyl dibasic sodium phosphate, Nakarai Tesque) (1mg/ml, 100 μ l/well) was added to each well to develop color. Microplatereader (MTP-120 microplatereader, Corona Electric) was
25 used for measurement (415 nm).

Quantitative measurement of IL-5 was done by a similar

method described above using rat anti-mouse-IL-5 antibody (Pharmingen, San Diego, CA, Code No. 18051D, 0.5 mg/ml) as a primary antibody and biotinated rat anti-mouse-IL5 antibody (Pharmingen, San Diego, CA, Code No. 18062D, 0.5 mg/ml) as a secondary antibody. Recombinant mouse IL-5 (Pharmingen, San Diego, CA, Code No. 19241W, 0.5 mg/ml) was used to make a calibration curve.

Quantitative measurement of IFN- γ was done by a similar method described above using rat anti-mouse-IFN- γ antibody (Pharmingen, San Diego, CA, Code No. 18181D, 0.5 mg/ml) as a primary antibody and biotinated rat anti-mouse-IFN- γ antibody (Pharmingen, San Diego, CA, Code No. 18112D, 0.5 mg/ml) as a secondary antibody. Recombinant mouse IFN- γ (Pharmingen, San Diego, CA, Code No. 19301U, 0.5 mg/ml) was used to make a calibration curve.

All experiments were done by triplicate and the means values were obtained.

2. Result

Results are shown in Table 1. Imiquimod strongly suppresses the production of IL-4 and IL-5 and outstandingly enhances the production of IFN- γ . Therefore it is revealed that Imiquimod has desired property of suppressing Th2 type immune response and enhancing Th1 type immune response.

Table 1

Concentration of Imiquimod (μ M)	Amount of cytokine production (ng/ml)		
	IL-4 (SD)	IL-5 (SD)	IFN- γ (SD)
0	24.0 (0.8)	18.8 (0.9)	10.4 (2.9)
1.56	24.9 (2.9)	23.6 (2.3)	8.6 (2.0)
3.13	26.6 (3.7)	19.0 (0.6)	19.3 (11.2)
6.25	9.2 (2.3)	12.4 (0.5)	41.7 (10.7)
12.5	3.0 (1.1)	9.3 (1.6)	32.3 (3.2)
25.0	1.2 (0.1)	5.7 (0.2)	28.0 (1.4)

Example 2

1. Method

Male 7 week-old BALB/c mice were sensitized by painting with 0.2 ml of 0.5 % acetone/dibutyl phthalate solution of fluoresceine isothiocyanate (hereinafter FITC) on the abdomen being shaved a day before the sensitization.

Seven days later, ear swelling was elicited by applying 20 μ l of 0.5 % acetone/dibutyl phthalate solution of FITC to each side of left ear.

24 hours later ear thickness was measured by micrometer, and the difference between before and after elicitation was studied. Test compound was suspended in 0.5 % carboxymethylcellulose and administered orally two hours before the elicitation.

2. Result

Effect of Imiquimod and dexamethasone on the FITC-induced DTH reactions in BALB/c mice

5	Compound	Dose (mg/kg p.o.)	Ear swelling (mm)	Inhibition (%)
	Control	-	0.120 ± 0.011	-
10	Imiquimod	10	0.082 ± 0.013	32
		30	$0.066 \pm 0.005^{**}$	45
	Dexamethasone	3	$0.070 \pm 0.008^{**}$	42
15				

** : $p < 0.01$, Mean \pm S.D. [n=6]

Example 3

1. Method

100 μ g of ovalbumin was adsorbed to 1.6mg of aluminum hydroxide gel (200 μ l) and the adsorbed aluminum hydroxide gel was immunized by subcutaneous administration to dorsum of male 8 week-old BALB/c mice. Seven days later the mouse was immunized by the adsorbed aluminium hydroxide gel again. Seven days after second immunization 10 μ g of ovalbumin in 200 μ l of saline was administered intraperitoneally. Two days after the intraperitoneal administration peritoneal exudated cells were collected by using saline. Total number of peritoneal exudated cells and eosinophils was measured by the method of staining by Turk solution and Hinkelman solution. Test compound was suspended in 0.5 % carboxymethylcellulose and administered orally (10 ml/kg) two hours before the third ovalbumin administration.

2. Result

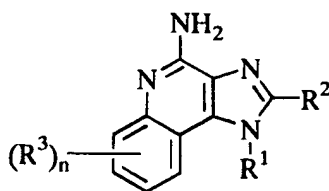
Effect of Imiquimod and dexamethasone on the antigen specific eosinophil infiltration to peritoneal cavity of BALB/c mice

5	Compound	Dose (mg/kg p.o.)	N	Cell number in peritoneal cavity		Eosinophil /
				Eosinophil ($\times 10^{-4}$)	Total cells($\times 10^{-4}$)	Total cells (%)
	Control (CMC)	-	4	64.8 \pm 12.0	500.5 \pm 35.5	12.7 \pm 1.6
	Imiquimod	30	3	13.9 \pm 0.7**	395.0 \pm 50.3	3.6 \pm 0.5**
10	Dexamethasone	3	3	45.5 \pm 4.7	411.3 \pm 18.8	10.3 \pm 0.7

** : p<0.01, Mean \pm S.D.

CLAIMS

1. A pharmaceutical composition for suppressing Th2 type immune response comprising a therapeutically effective amount of a compound represented by the formula (1):



- wherein R^1 is a straight or branched chain alkyl having 1 to 10 carbon atoms; a cycloalkyl having 3 to 7 carbon atoms; a hydroxyalkyl having 1 to 6 carbon atoms; an acyloxyalkyl wherein the alkyl moiety has 1 to 6 carbon atoms and the acyloxy moiety is an alkanoyloxy having 2 to 4 carbon atoms or benzyloxy; an aralkyl; a substituted aralkyl; a phenyl; or a substituted phenyl;
- R^2 is hydrogen atom or an alkyl having 1 to 8 carbon atoms;
- R^3 is an alkoxy having 1 to 4 carbon atoms, a halogen atom or an alkyl having 1 to 4 carbon atoms; and
- n is an integer from 0 to 2; or a pharmaceutically acceptable acid salt thereof in admixture with a conventional pharmaceutically acceptable carrier or diluent.

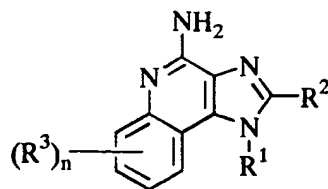
2. The pharmaceutical composition as claimed in claim 1 wherein R^1 is 2-methylpropyl or 2-hydroxy-2-methylpropyl.

3. The pharmaceutical composition as claimed in claim 1 or 2 wherein R^2 is hydrogen, or methyl.

4. The pharmaceutical composition as claimed in claim 1, 2 or 3 wherein n is 0.

5. A pharmaceutical composition for suppressing Th2 type immune response comprising a therapeutically effective amount of 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine or a pharmaceutically acceptable acid salt thereof in admixture with a conventional pharmaceutically acceptable carrier or diluent.

6. A method of treating or preventing a disease caused by abnormal activation of Th2 type immune response comprising administering a therapeutically effective amount of a compound represented by the formula (1):



wherein R¹ is a straight or branched chain alkyl chain having 1 to 10 carbon atoms ; a cycloalkyl having 3 to 7 carbon atoms; a hydroxyalkyl having 1 to 6 carbon atoms; an acyloxyalkyl wherein the alkyl moiety has 1 to 6 carbon atoms and the acyloxy moiety is an alkanoyloxy having 2 to 4 carbon atoms or benzoyloxy; an aralkyl; a substituted aralkyl; a phenyl; or a substituted phenyl;

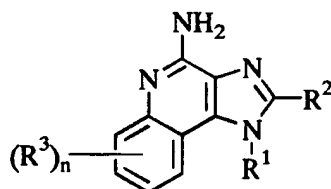
R² is hydrogen atom or an alkyl having 1 to 8 carbon atoms;

R³ is an alkoxy having 1 to 4 carbon atoms, a halogen atom or an alkyl having 1 to 4 carbon atoms; and

n is an integer from 0 to 2; or a pharmaceutically acceptable acid salt thereof to a patient in need thereof.

7. A pharmaceutical composition for treating or preventing an allergic disease or an autoimmune disease caused by abnormal activation of Th2 type immune response comprising a therapeutically

effective amount of a compound represented by the formula (1):



wherein R¹ is a straight or branched chain alkyl having 1 to 10 carbon atoms; cycloalkyl having 3 to 7 carbon atoms; a hydroxyalkyl having 1 to 6 carbon atoms; an acyloxyalkyl wherein the alkyl moiety has 1 to 6 carbon atoms and the acyloxy moiety is an alkanoyloxy having 2 to 4 carbon atoms or benzoyloxy; an aralkyl; a substituted aralkyl; a phenyl; or a substituted phenyl;

R² is hydrogen atom or an alkyl having 1 to 8 carbon atoms;

R³ is an alkoxy having 1 to 4 carbon atoms, a halogen atom or an alkyl having 1 to 4 carbon atoms; and

n is an integer from 0 to 2; or a pharmaceutically acceptable acid salt thereof in admixture with a conventional pharmaceutically acceptable carrier or diluent.

8. The pharmaceutical composition as claimed in claim 7 wherein a disease caused by abnormal activation of Th2 type immune response is asthma, allergic dermatitis, allergic rhinitis or systemic lupus erythematosus.

9. The pharmaceutical composition as claimed in claim 7 or 8 in which the active ingredient is 1-(2-methylpropyl)-1H-imidazo-[4,5-c]quinolin-4-amine or a pharmaceutically acceptable acid salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/01841

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 05042 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 18 March 1993 see page 16	1-9
X	--- R.L.MILLER ET AL.: "Cytokine induction by imiquimod" CHEMOTHER.J., vol. 4, no. 3, August 1995, pages 148-150, XP002073158 see abstract	1-9
X	--- M.J.REITER ET AL.: "Cytokine induction in mice by the immunomodulator imiquimod" J.LEUKOC.BIOL., vol. 55, no. 2, February 1994, pages 234-240, XP002073159 see abstract --- -/-	1-9

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

30 July 1998

Date of mailing of the international search report

27/08/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Theuns, H

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/01841

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	T.L.TESTERMAN ET AL.: "Cytokine induction by the immunomodulators imiquimod and S-27609" J.LEUKOC.BIOL., vol. 58, no. 3, September 1995, pages 365-372, XP002073160 see abstract ---	1-9
X	P.SAVAGE ET AL.: "A phase I clinical trial of imiquimod, an oral interferon inducer, administered daily" BR.J.CANCER, vol. 74, no. 9, November 1996, pages 1482-1486, XP002073161 see abstract ---	1-9
X	P.L. WITT ET AL.: "Phase I Trial of an Oral Immunomodulator and Interferon Inducer in Cancer Patients" CANCER RES., vol. 53, no. 21, 1 November 1993, pages 5176-5180, XP002073162 see abstract ---	1-9
X	K.MEGYERI ET AL.: "Stimulation of Interferon and Cytokine Gene Expression by Imiquimod and Stimulation by Sendai Virus Utilize Similar Signal Transduction Pathways" MOL.CELL.BIOL., vol. 15, no. 4, April 1995, pages 2207-2218, XP002073163 see abstract ---	1-9
A	& K.MEGYERI ET AL.: "ERRATA" MOL.CELL.BIOL., vol. 15, no. 5, May 1995, page 2905 ---	1-9
X	S.J.GIBSON ET AL.: "Cellular Requirements for Cytokine Production in Response to the Immunomodulators Imiquimod and S-27609" J.INTERFERON CYTOKINE RES., vol. 15, no. 6, June 1995, pages 537-545, XP002073164 see abstract ---	1-9
X	C.E.WEEKS ET AL.: "Induction of Interferon and Other Cytokines by Imiquimod and Its Hydroxylated Metabolite R-842 in Human Blood Cells In Vitro" J.INTERFERON RES., vol. 14, no. 2, April 1994, pages 81-85, XP002073165 see abstract --- -/--	1-9

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/01841

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 145 340 A (RIKER LABORATORIES, INC.) 19 June 1985 see claim 1 ---	1-9
Y	WO 92 15582 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 17 September 1992 see page 18 ---	1-9
Y	K.KARACA ET AL.: "In Vivo and In Viro Interferon Induction in Chickens by S-28828, an Imidazoquinolinamine Immunoenhancer" J.INTERFERON CYTOKINE RES., vol. 16, no. 4, April 1996, pages 327-332, XP002073166 see abstract -----	1-9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 98/01841

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 6
because they relate to subject matter not required to be searched by this Authority, namely:
See FURTHER INFORMATION SHEET PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claim 6 is directed to a method of treatment of the human/animal body, the search has been based on the alleged effects of the compound/ composition. the expressions "suppressing Th2 type immune response" and "a disease caused by abnormal activation of Th2 type immune response" are not adequate descriptions relating to defined therapeutic applications, because it is not immediately clear which therapeutic applications are related to such concepts.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 98/01841

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9305042 A	18-03-1993	US 5268376 A	07-12-1993
		AU 2514792 A	05-04-1993
		CA 2116782 A	18-03-1993
		CZ 281726 B	11-12-1996
		CZ 9400487 A	13-07-1994
		EP 0603251 A	29-06-1994
		HU 67398 A	28-04-1995
		HU 69407 A	28-09-1995
		HU 9500663 A	28-11-1995
		IL 102951 A	30-09-1997
		JP 6510299 T	17-11-1994
		MX 9205046 A	01-03-1993
		NZ 244075 A	26-05-1995
		US 5525612 A	11-06-1996
		US 5714608 A	03-02-1998
		US 5346905 A	13-09-1994
		ZA 9206456 A	04-03-1993
EP 0145340 A	19-06-1985	AU 2991189 A	15-06-1989
		AU 581190 B	16-02-1989
		AU 3540284 A	23-05-1985
		CA 1271477 A	10-07-1990
		DE 3486043 A	25-02-1993
		DK 135791 A	16-07-1991
		DK 135891 A, B,	16-07-1991
		DK 135991 A, B,	16-07-1991
		DK 136091 A, B,	16-07-1991
		DK 136191 A, B,	16-07-1991
		DK 542684 A, B,	19-05-1985
		EP 0310950 A	12-04-1989
		JP 1874785 C	26-09-1994
		JP 60123488 A	02-07-1985
		US 4698348 A	06-10-1987
		MX 9203474 A	01-07-1992
		US 4689338 A	25-08-1987
WO 9215582 A	17-09-1992	AU 658621 B	27-04-1995
		AU 1566992 A	06-10-1992
		AU 673309 B	31-10-1996
		AU 2715795 A	21-09-1995

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/JP 98/01841

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9215582 A		CA 2104782 A	02-09-1992
		CZ 9301788 A	18-10-1995
		EP 0582581 A	16-02-1994
		HU 67026 A	30-01-1995
		HU 211242 B	28-11-1995
		IL 101110 A	08-12-1995
		IL 114570 A	31-10-1996
		JP 6504789 T	02-06-1994
		NO 933069 A	01-11-1993
		NZ 241784 A	27-06-1995
		SG 46492 A	20-02-1998
		US 5605899 A	25-02-1997
		US 5741909 A	21-04-1998
		US 5389640 A	14-02-1995